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# THE U.S. EPA'S DRAFT ETS RISK ASSESSMENT

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The U.S. Environmental Protection Agency's draft risk assessment on exposure to environmental tobacco smoke (ETS), together with its companion document, a draft ETS workplace policy guide, was released for public comment in June 1990. The draft concludes that ETS is a Group A or "known human" carcinogen on the basis of 24 published epidemiologic studies relating to lung cancer incidence in non-smokers married to smokers. The draft concludes in addition that some 3800 Americans die every year from lung cancer caused by exposure to ETS. The great majority of scientists who filed comments with EPA were severely critical of the agency's efforts, however.

## I. FLAWS IN THE EPA DRAFT

Of the many flaws addressed in the public comments, several key points highlight the total lack of scientific justification for the claims about ETS exposure that are contained in the EPA draft.

First, the EPA draft constitutes the agency's first effort to conduct a risk assessment based entirely on epidemiologic

evidence. The epidemiologic studies reviewed by EPA do not, however, support the determination that ETS is a cause of lung cancer in non-smokers. For example, of the 24 published studies on spousal smoking and non-smoker lung cancer, the vast majority (19) have reported no statistically significant elevated risk associated with ETS exposure. Additionally, those few studies that have reported a statistically significant association between non-smoking spouses and lung cancer report risk ratios that are weak at best - all within the range that epidemiologists in general consider difficult to interpret because of problems inherent in study design and conduct.

Second, the draft report applies the controversial statistical tool of "meta-analysis", which combines a body of disparate epidemiologic studies to produce a single estimate of relative risk. This technique is used incorrectly, however. For example, several studies - all reporting no statistically significant association between marriage to a smoker and risk of lung cancer - were omitted from the calculations. Also, the draft fails to calculate risk on the basis of the U.S. studies alone, despite the fact that it purports to estimate risk for the U.S. population. None of the nine existing U.S. studies has reported a statistically significant association between spousal smoking and lung cancer. In addition, combination of the U.S. and non-U.S. studies is unjustified because ETS exposure levels, study bias and lifestyle factors can vary greatly across different cultures. Furthermore, the discrepancy between a

meta-analysis of the U.S. studies (reporting no significant increase in risk) and certain of the non-U.S. studies is a serious inconsistency that casts further doubt on the draft document.

Third, the reported risk in the EPA draft is inconsistent with other evidence. For example, the draft asserts that ETS exposure causes more than one-fourth of all female non-smoker lung cancer deaths. If this assertion were correct, actual female non-smoker lung cancer rates should have followed trends in cigarette sales and male smoking rates. There has, however, been no substantial increase in female non-smoker lung cancer rates since 1950. Also, if the standard EPA method of risk estimation is employed (that of extrapolating from effects observed at higher exposures to predicted effects at low exposures), a risk estimate is produced that is two to three orders of magnitude lower than the estimate in the draft risk assessment. This additional inconsistency undermines confidence in the validity of the agency's epidemiology-based conclusions.

Likewise, the chapter of the risk assessment dealing with respiratory health issues is seriously flawed. As a number of leading researchers pointed out in their submissions to the EPA, the studies conducted to date have not demonstrated that ETS is a cause of acute or chronic respiratory problems in adults or children.

As far as the EPA's draft workplace policy guide is concerned, many of the same scientific concerns were raised about this document during the public comment process. In addition, a number of experts have pointed out that private as well as governmental studies have concluded that smoking seldom contributes to the so-called "sick building" syndrome, and proper ventilation rather than smoking bans or severe restrictions is the key to meaningful improvements in indoor air quality. Since there are in any event inadequate data on ETS in the workplace, and since the risk assessment document cannot be scientifically supported, workplace guidelines from the EPA are inappropriate.

In sum, a careful scientific review of the evidence reveals that the EPA draft documents on ETS are an uncritical condensation of only selected studies from the scientific literature. The selectively chosen studies were then subjected to a series of highly speculative adjustments, seemingly to reach "a predetermined outcome".

The fact that EPA has chosen to prepare an ETS risk assessment and policy guide is surprising when one considers that the vast majority of the published studies - including all of the U.S. studies - have not reported a statistically significant association between ETS exposure and non-smoker lung cancer and that the evidence on ETS and respiratory health is so equivocal. Given the inconsistencies and weaknesses in the data, it is not reasonable to infer that ETS exposure causes lung cancer or other

respiratory problems, let alone to attempt to quantify or predict risk.

## II. ETS LUNG CANCER EPIDEMIOLOGY

The draft ETS risk assessment is the first risk assessment ever conducted by EPA that is based entirely on epidemiologic evidence. Epidemiology is an observational science concerned with the search for associations between agents and disease through organized collection and analysis of data about human populations. ETS epidemiologic studies thus far have involved comparisons of lung cancer risk between non-smokers married to non-smokers (therefore presumed not to be exposed to ETS) and non-smokers married to smokers (presumed to be exposed to ETS).

A review of the published ETS-lung cancer studies reveals the following:

- A total of 21 case-control (or "retrospective") and 3 cohort (or "prospective") studies of spousal smoking and non-smoker lung cancer are listed in the ETS report. Of those, only five have reported a statistically significant association.

- Of nine U.S. studies, none - not even the largest case-control study ever conducted in the U.S. - has

reported a statistically significant association between spousal smoking and lung cancer.

o Even those studies that have reported statistically significant associations between spousal smoking and lung cancer report risk ratios that are weak at best - all well below 3.0. Epidemiologists agree that studies reporting such weak associations are difficult to interpret because of the problems inherent in the design and conduct of observational studies.

o All of the existing epidemiologic studies of ETS and lung cancer - and particularly the Hirayama study, which carries great weight in the ETS meta-analysis - suffer from a variety of serious flaws. These include in particular:

- Poor exposure classification: Because the ETS epidemiology is based on reports of spousal smoking, the actual existence or degree of non-smoker exposure is unknown.

- Inadequate attention to confounding factors: Confounding factors are lifestyle characteristics that are common to both the agent and the disease under study and which therefore could create an apparent association where none in fact exists.

In the case of ETS, a confounding factor is one that is common to marriage to a smoker and to lung cancer. Diet is one example: if smokers tend to have poorer diets than non-smokers, if a non-smoker married to a smoker may be expected to share the poorer diet, and if diet is associated with lung cancer, then an effect mistakenly attributed to ETS may in fact be due to diet instead. Other potential confounding factors include alcohol consumption, occupational exposures and socio-economic status.

## III. META-ANALYSIS

Meta-analysis is a statistical procedure in which a number of studies are combined to produce a single estimate of relative risk. Meta-analysis generally is used when studies standing alone lack sufficient statistical power (i.e. do not deal with a sufficient number of cases) to justify the interpretation of an association.

The meta-analysis conducted in the ETS risk assessment is flawed for several reasons. First, although a total of 22 case-control studies on ETS and lung cancer have been conducted to date, only 19 were included in the EPA's meta-analysis of ETS studies. The three studies omitted from the calculations are the Shimizu et al. and Sobue et al. studies from Japan and the Varela

study from the U.S. None of these studies reported a statistically significant association between marriage to a smoker and risk of lung cancer.

EPA claims that the Varela and Shimizu studies were omitted because raw data were not available. However, a number of researchers have noted that the missing data can be obtained through statistical analysis of the data provided, with less uncertainty than is produced by many other of the EPA risk assessment's assumptions. Although the Sobue study was published following release of the draft ETS risk assessment, EPA should revise its meta-analysis to include all currently available data.

Exclusion of the Varela study is particularly disturbing since, unlike many of the studies in the ETS database, it is directly relevant to the U.S. population. The Varela study also is the largest case-control study ever conducted in the U.S.

Second, the draft EPA report makes no effort to compare U.S. with non-U.S. studies, despite the fact that the risk assessment purports to estimate risk for the U.S. population. A meta-analysis computed for the U.S. studies alone demonstrates no statistically significant association between ETS and lung cancer. The relative risk calculated through a meta-analysis of the nine U.S. studies (eight case-control and one cohort) is 1.08 and is not statistically significant.

## IV. DISCREPANCIES IN THE EVIDENCE

Not only do the epidemiologic studies of ETS and lung cancer fail to demonstrate a convincing association, but other evidence refutes the assertion that ETS is a cause of non-smoker lung cancer. First, the standard method of risk estimation employed by EPA - the dosimetric approach, or extrapolating to low exposures from effects observed at higher exposures - produces a risk estimate for ETS that is two to three orders of magnitude lower than the estimate derived from a review of the epidemiologic studies. This greatly undermines confidence in the validity of the EPA's epidemiology-based conclusions. Second, the EPA draft's assertion that ETS causes more than one-fourth of all female non-smoker lung cancer deaths cannot be reconciled with national cancer mortality statistics. If ETS were a cause of lung cancer in female non-smokers, then female non-smoker lung cancer rates should have followed the rise and fall of cigarette sales and of male active smoker lung cancer rates. In fact, there has been no substantial increase in female non-smoker lung cancer rates since 1950.

## V FAILURE TO FOLLOW EPA GUIDELINES FOR ASSESSMENT OF CARCINOGENS

The draft ETS risk assessment is the first risk assessment ever conducted by EPA that is based entirely on epidemiologic evidence. This particular risk assessment also involves the most

difficult issues in epidemiology: weak associations, indirect and unreliable measures of exposure, extremely low-level exposures, long latency periods for the disease in question, and numerous possible sources of bias and confounding.

Given the unprecedented nature of this risk assessment and the many difficult issues involved, it is surprising that EPA did not attempt an independent critical evaluation of the individual epidemiologic studies. EPA's failure to provide a thorough critique completely ignores the recommendations of a panel of distinguished epidemiologists convened at EPA's request to issue guidelines for the assessment of carcinogens based on human data. These recommendations, outlined in a 1989 report, acknowledge the difficulty of interpreting human data and call for application of criteria in evaluating epidemiologic studies that the EPA has chosen to ignore.

The seven criteria outlined in the 1989 EPA report for assessing study adequacy include proper selection and characterization of study and comparison groups, adequacy of response rates and methodology for handling missing data, clear and appropriate methodology for data collection and analysis, proper identification and characterization of confounding factors and bias, appropriate consideration of latency effects, valid ascertainment of the causes of morbidity and death, and summary weight of evidence criteria. The draft EPA report makes no effort to apply these criteria on a study-by-study basis despite

the fact that virtually all of the ETS-lung cancer studies fail on a number of these considerations.

The criteria outlined in the 1989 EPA report to support a judgment of cause and effect from an epidemiologic data set include consistency of association, strength of association, presence of a temporal relationship, presence of a dose response or biological gradient, specificity of the association, biological plausibility, and collateral evidence. Although it makes no sense to apply these criteria when the criteria for study adequacy have not been met - as they have not been in the ETS literature - EPA also has failed to address the many insufficiencies in the ETS database with regard to these crucial issues.

It is also significant that the conclusions in the EPA draft risk assessment show that the agency is applying its carcinogen classification guideline inconsistently. As the attached chart demonstrates, for example, the agency concluded in its recent draft risk assessment on exposure to electromagnetic fields (EMF) that such exposure could not be viewed as causing cancer. And yet the data base on EMF exposure discussed in that document was in numerous respects <u>stronger</u> than that for ETS exposure.

## VI RESPIRATORY EFFECTS IN CHILDREN AND ADULTS

A chapter of the draft risk assessment concludes that parental smoking is associated with an increased incidence of respiratory diseases and symptoms in children and with reduction in certain pulmonary function parameters. Based on a review of the relevant literature, however, scientists with relevant expertise have concluded that the reported statistical associations between ETS and respiratory symptoms, disease and pulmonary function effects in children frequently are inconsistent and could be due to factors other than ETS, such as variability in adjustment for confounding factors including socioeconomic status, occupational exposures, history of respiratory illness and use of gas stoves in the home; or unreliability of clinical data, particularly errors due to lack of verification.

As a general matter, the draft risk assessment's chapter on respiratory effects in children displays a number of flaws that make it an unreliable document. It is incomplete in that it omits significant scientific references. It is superficial in that it oversimplifies data and concepts, and it fails to review the relevant studies critically. It is inaccurate in reporting and interpreting the relevant literature. It lacks objectivity, as shown by its selective dismissal of statistical testing standards and de-emphasis of key confounding variables.

In addition, contrary to assertions in the draft ETS policy guide, there is no conclusive evidence that ETS exposure affects conditions such as asthma, emphysema and bronchitis. Likewise, the policy guide suggests that allergies may be aggravated by ETS exposure. The U.S. Surgeon General's 1986 report and the 1986 National Research Council report both noted that the data available at that time did not support such an assumption. No studies appearing since 1986 justify departing from the negative conclusion of those reports.

## VII. THE REVIEW PROCESS

The EPA's draft ETS documents have been subjected to review by a committee of the agency's Science Advisory Board (SAB), a body set up in accordance with a federal statute that consists of scientists outside of the agency who provide advice on scientific and technical issues at the agency's request.

An SAB committee met in Washington on December 3 and 4, 1990 to consider the draft ETS documents. Supposedly the panel members had been provided not only with the draft documents themselves but with copies of extensive scientific comments that had been submitted to the agency. In addition, part of the meeting was devoted to presentations by members of the public on the merits of the documents. Curiously, it became clear that a number of panel members had little familiarity with the issues raised in the public comments and some even stated on the record

that they had received copies of such comments from the agency but had not bothered to look at them. In addition, while the meeting agenda presented an opportunity for panel members to put questions to those presenting oral comments, the presentations typically were heard in silence with not even a flicker of interest from the panel members. Nevertheless, the Chairman insisted that the meeting proceed rapidly, so rapidly that a number of scheduled public comments were deleted entirely from the program. And yet the meeting concluded well ahead of schedule.

At the conclusion of the meeting, the Chairman called a brief press conference at which he announced that the consensus of the committee was that there was adequate evidence on which to base a judgment that ETS is a Group A or "known human" carcinogen. He stated, however, that the EPA staff had not in fact "made the case" for this conclusion in its current draft document. Indeed, the view he expressed in the press conference, together with the discussion by panel members over the course of the two-day meeting, lead one to believe that the committee takes the position that the extant epidemiologic studies, standing alone, do not justify a carcinogen assessment, much less a precise prediction of lung cancer incidence in the U.S. population. The Chairman's position, however, appeared to be that one could simply assume, on the basis that ETS and mainstream tobacco smoke (MSS) were essentially the same, that

epidemiologic and toxicologic data concerning the latter could somehow be applied to the former.

This conclusion ignores the extensive comments submitted to the committee demonstrating that ETS and MSS are in fact not equivalent substances, and that one cannot simply extrapolate from one to the other. It also ignores the agency's own guidelines that require that there be adequate human (i.e. in this case epidemiologic) data before a substance can be labelled a known human carcinogen. Further, the notion that the committee had reached a consensus on this critical point is curious in view of the fact that many panel members expressed serious doubts about the adequacy of the data. In particular, Dr. Kabat - the one panel member who had himself conducted epidemiologic work on ETS in the United States (with negative results), who summed up his views at the meeting by stating that classifying ETS as a known human carcinogen would be "rash".

Thus, it is unclear what the SAB's recommendations to EPA will be when it submits the report of its committee. If the SAB rejects the method used by EPA in the current draft to reach its carcinogen classification decision, but still believes that such a decision can appropriately be reached, then it presumably will offer guidance on how to do so. And yet, there appears to be no way in which to apply the agency's current carcinogen classification guidelines to the data at hand and reach the conclusion that the agency seems to want to reach.

## VIII. A EUROPEAN PERSPECTIVE

The EPA's draft ETS lung cancer risk assessment concludes, on the basis of a meta-analysis of a group of epidemiologic studies, that ETS is a known human carcinogen and that exposure to ETS causes over 3000 lung cancer deaths in the United States each year. The agency attempts to bolster its conclusions by relying on a general notion of "biological plausibility", which in turn assumes that exposure to ETS can be equated with a low-dose exposure to mainstream tobacco smoke and that there is no "safe" threshold for such exposure.

The clear majority of scientific comments filed with EPA with respect to the draft risk assessment refuted the agency's conclusions. Among these comments are a considerable number of contributions by eminent European scientists. Among the key conclusions reached by these scientists are the following:

- Professor B. Schneider, of the Institute of Biometry of the medical school in Hanover, Germany, reanalyzed the data employed by the authors of the ETS epidemiologic studies and concluded that "a valid statistical analysis does not reveal any significant association between ETS and any health risks". In particular, with regard to meta-analysis he concluded that the flaws in the individual studies did not justify employing the technique: "Combining a number of poor results does not

improve their quality. The 'combined' result is as poor as the single results."

- Peter Skrabanek, Senior Lecturer on Community Health at Trinity College, Dublin, questioned EPA's heavy reliance on its meta-analysis of epidemiologic studies (especially that by Hirayama) carried out on Asian women: "Such women are unsuitable for studying the effects of ETS, given evidence of strong confounding factors and because even active smoking in these women has been only weakly associated with lung cancer and the majority of lung cancer cases are non-smokers." Further, he detected "serious unresolved problems of biological plausibility" in the EPA draft, pointing out in particular that "[i]t is counter-intuitive to accept at face value reports, such as Hirayama's, claiming that the lung cancer risk from passive smoking is very similar to that of active smoking."

- United Kingdom statistician Peter Lee - to whose work the EPA draft made numerous references - provided an exhaustive analysis of every epidemiologic study conducted with respect to ETS exposure and lung cancer. The key flaws he detected in the EPA draft, which in his view rendered it "unacceptable", were its "overestimation of epidemiological in relation to dosimetric evidence", its "omission of relevant data

and inclusion of inappropriate data in the meta-analysis of the epidemiological evidence", its "errors in adjustments for bias due to misclassification of smoking habits", and its "errors in applying the adjusted meta-analysis risk estimates".

- Professor Guy Crepat, head of the Applied Biology Department at the University of Burgundy in France, disputed the EPA draft's reliance on an assumed linear relation between cancer risk from ETS exposure and the level of concentration of cotinine (a metabolite of nicotine) in the body fluids of non-smokers, and demonstrated that such reliance leads inevitably to an overestimation of risk.

- Professor Ragnar Rylander of the Department of Environmental Hygiene at the University of Gothenburg in Sweden focused his attention on the issue of biological plausibility. He pointed out that the average exposure to tobacco smoke constituents in ETS-exposed individuals is exceedingly low, thus providing grounds for scepticism about a causal relationship with respect to lung cancer. Likewise, he disputed the EPA's assertion of a linear dose-response relationship for ETS exposure. In summary, he offered the judgment that "the arguments for biological plausibility in the [EPA draft] unfortunately do not

reflect a critical scientific evaluation of the critical toxicological and epidemiological concepts involved."

- R.C. Brown of the Medical Research Council Toxicology Unit in the United Kingdom cautioned that the acceptance of the EPA draft's unfounded conclusions could lead to the misattribution to ETS exposure of many lung cancer cases that are in fact due to other, as yet unidentified, causes.

- Professor J.W. Daniel of Kings College, London, reviewed the evidence on which the EPA draft is based and concluded that "the scientific criteria that must be met to conclude that ETS induces pulmonary tumours either in experimental animals or in man following inhalation have not been met." In his view, acceptance of the EPA's report will present the danger of "inhibiting further research into those genetic and environmental factors that have been implicated in the aetiology of lung cancer."

- Dr. John Faccini, a practising histopathologist and Professor of Pathology at the University of Surrey, criticized the EPA draft for its heavy reliance on epidemiologic studies where the diagnosis of lung cancer was not adequately confirmed

histopathologically. This leads to the risk that a significant portion of the apparent lung cancer cases on which the ETS epidemiology is based in fact did not originate in the lung but were metastatic, i.e. originating elsewhere and spreading to the lung.

- United Kingdom pathologist F.J.C. Roe, formerly head of the Department of Experimental Pathology at the London Institute of Cancer Research, took the EPA draft to task in particular for its "wholly unscientific and wholly invalid" use of meta-analysis and expressed the view that "the only safe conclusion that can be based on the available evidence is that it remains unclear whether there is any lung cancer risk from exposure to other people's tobacco smoke and that if there is any such risk there is absolutely no reliable way to quantify it."

From the foregoing it will be seen that there is a considerable body of scientific thought in Europe - as, indeed, there is in the United States - that places no credence in the conclusions of the EPA's draft ETS risk assessment. In the view of these scientists, ETS exposure has not been proved to cause any adverse health effects.